PHILIP MORRIS U. S. A.

INTER-OFFICE CORRESPONDENCE

Richmond, Virginia

PERSONAL AND CONFIDENTIAL

To: R. A. Carchman Date: May 22, 1990

From: F. P. Gullotta, C. S. Hayes and B. R. Martin

Subject: **Stereospecific Effects of Nicotine on Electrophysiological and Subjective Responses**

Summary

The electrophysiological and subjective effects of smoking ART cigarettes containing either d, l, or dl-nicotine were studied in fifteen volunteers. Cigarettes containing only d-nicotine could not be electrophysiologically or subjectively differentiated from ART controls. Cigarettes containing dl-nicotine produced subjective effects intermediate to those produced by l-nicotine cigarettes and to those produced by control cigarettes. However, cigarettes containing dl-nicotine produced electrophysiological effects comparable to those produced by cigarettes containing twice the amount of l-nicotine. These data suggest that, although d-nicotine itself is inactive, it synergistically interacts with l-nicotine, enhancing the effects of the latter.

Informal observations have led to the tentative conclusion that the sensory properties of d- and l-nicotine are quite different. When smelled, d-nicotine is virtually devoid of the pungency which is the dominant feature of its stereoisomer. When smoked, d-nicotine yields none of the impact normally associated with l-nicotine. Are these sensory differences indicative of electrophysiological differences between d- and l-nicotine?

Although a great deal is known about the central nervous system (CNS) and behavioral properties of l-nicotine, relatively little is known about its stereoisomer. Most studies tend to show that d-nicotine produces behavioral effects which are qualitatively similar to l-nicotine,[1] [2] implying that similar CNS mechanisms are involved. However, depending on the types of behavioral tests that are employed, the d- isomer has usually been found to be considerably less potent. Still other studies have shown that d- and l-nicotine produce qualitatively different effects,[3] implying that the two isomers are influencing different CNS mechanisms.

2022198661

C90-08106

The current study explored the relationship between d- and l-nicotine in cigarette smoke employing pattern-reversal evoked potentials (PREPs) and subjective evaluations. Specifically, the study compared the electrophysiological and subjective effects produced by smoking cigarettes containing equimolar amounts of either d- , l-, or dl-nicotine.

The cigarettes that were employed in the study were four 8.0 mg tar/cigt ART-extracted models. Three of the models were hand-injected with equal amounts of either d-, l-, or dl-nicotine.[4] [5] The fourth sample (control) was not injected.

To ensure an equal distribution of nicotine in the cigarettes, filler from each of the injected models was removed and mixed. Hand-made cigarettes were then prepared, once again using 8.0 mg tar ART blanks. Filler analyses were conducted by the Analytical Research Division and revealed that the d-, l-, dl-nicotine cigarettes contained 1.99, 1.96 and 2.08 percent nicotine, respectively.[6]

Fifteen R&D smokers served as subjects for the study. The mean tar and nicotine deliveries of the cigarettes that the subjects normally smoked was 10.63 (S.D.=3.65) mg/cigt and 0.80 (S.D.=0.25) mg/cigt, respectively.

The subjects were instructed to abstain from smoking for two hours and from caffeine for one hour prior to testing. A double-blind experiment was employed, where neither the subjects nor the experimenters were informed about which cigarette was being tested. Order of smoking of the four cigarettes was randomized for each subject.

All subjects smoked each cigarette using a controlled smoking procedure.[7] The controlled smoking procedure minimizes both inter- and intra-subject variability with respect to how cigarettes are smoked. In the current study, the subjects were required to take seven puffs (excluding the lighting puff, which was not inhaled) on each cigarette. The inter-puff interval was held at 30 sec.

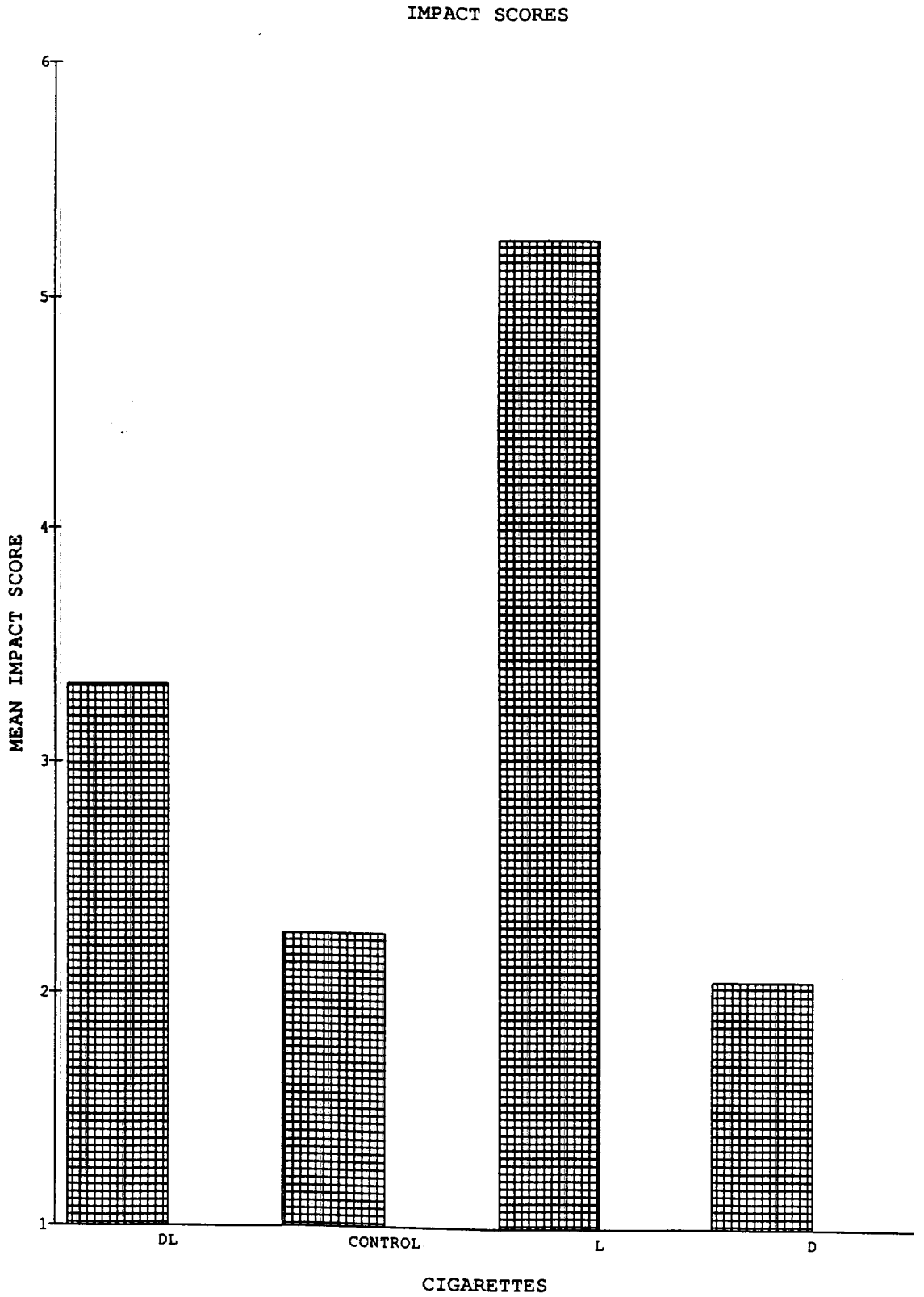
Pre- and post-smoking PREPs were recorded from two scalp loci. One electrode was positioned over midline occipital cortex (i.e., O_z) while the second electrode was positioned over midline parietal cortex (i.e., P_z).[8] The PREP waveform components that were measured included P_0, N_1, P_1 and N_2 latencies and P_0-N_1, N_1-P_1 and P_1-N_2 amplitudes. The data obtained from these measures were analyzed using repeated-measures analyses of variance (ANOVAs) and post-hoc multiple comparisons tests. Only P_1 latency data at O_z will be discussed in this report.

At the end of each experimental session the subjects were required to complete a flavor ballot (seven point scale) evaluating the cigarette that was smoked. The ballot contained seven items relating to liking, flavor and impact. These data were also analyzed using repeated-measures ANOVAs and post-hoc multiple comparisons tests.

Analyses of the subjective data confirmed the initial observations that d- and l-nicotine are different. For example, mean impact scores for the l-, dl-, and d-nicotine and control cigarettes were 5.27, 3.33, 2.07 and 2.27, respectively (see Figure 1). An ANOVA indicated that these means are not equal ($p < .0001$). Post-hoc multiple comparisons to determine which means were statistically different revealed that the l-nicotine cigarette was different ($p < .05$) from the dl-nicotine cigarette and that the dl-nicotine cigarette was different ($p < .05$) from the d-nicotine cigarette and the control. The d-nicotine cigarette and the control were not statistically different ($p > .05$). In other words, these data suggest that, in terms of impact, a cigarette containing d-nicotine cannot be differentiated from a cigarette without nicotine.

Statistically significant ($p < .004$) differences in liking scores were also obtained. The results indicated that the d-nicotine cigarette and the control were liked less than the l- and dl-nicotine cigarettes. Similar results were obtained from an analysis of satisfaction scores. No other subjective measure yielded statistically significant differences (p all $> .05$).

Figure 1



The figure illustrates mean (n=15) impact scores for the d, l, dl and control cigarettes. Scores for the d and control cigarettes are not statistically different ($p > .05$). All other comparisons are statistically different (p (all) $< .05$).

Overall, the subjective data suggest that d-nicotine is a relatively inactive compound. The electrophysiological data, however, indicate that d-nicotine in the presence of its stereoisomer is, indeed, active. Specifically, the mean post-smoking P_1 latency effects obtained for the control, d-, l- and dl-nicotine cigarettes were 0.11, -0.33, -1.89 and -2.39 msec, respectively (see Figure 2). These latency differences are statistically significant ($p < .001$). Post-hoc multiple comparisons tests show that the control and the d- cigarettes are not statistically different ($p > .05$). Also, the l- and the dl- cigarettes are not statistically different ($p > .05$). However, the l- and dl- cigarettes are statistically different ($p < .05$) from the control and the d- cigarettes.

These findings indicate that, although d-nicotine, by itself, has no effects on P_1 latency, it interacts with its stereoisomer to produce a synergistic effect. That is, there was half the amount of l-nicotine in the dl-nicotine cigarette, but it produced P_1 latency effects comparable to those obtained in the l-nicotine cigarette.

In summary, the data from the current study indicated that d-nicotine, in the amounts tested, had no effect on the subjective characteristics of ART cigarettes. The data also indicated that d-nicotine, by itself, was electrophysiologically inactive. However, it was found that d-nicotine enhanced the electrophysiological effects of l-nicotine.

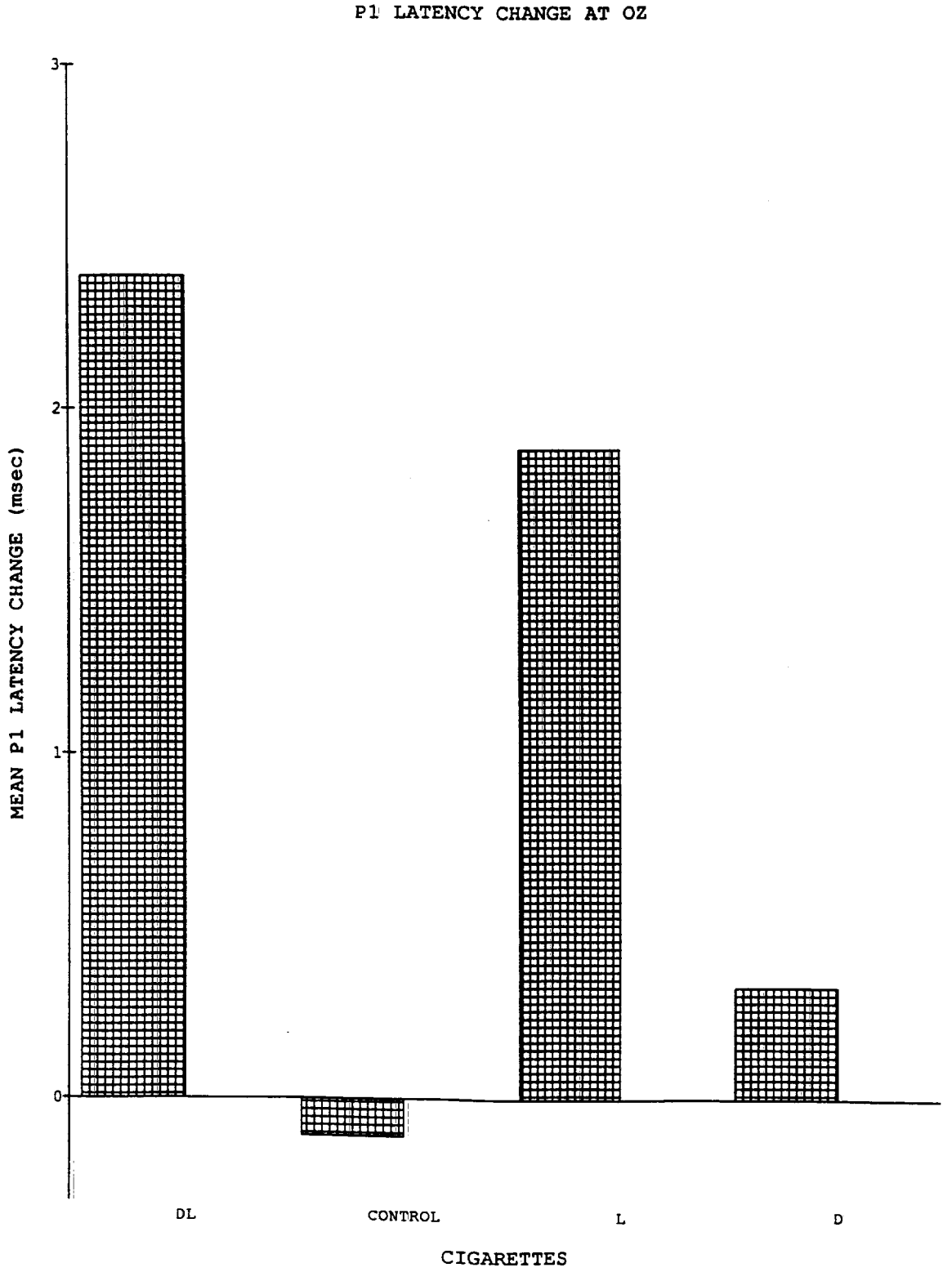
Acknowledgment

Project 1620 gratefully acknowledges the following individuals for their assistance in preparing the cigarettes for this study: R. Southwick, J. Seeman, H. Secor, J. Paine, N. McGee and R. Hellams.

/mps

cc: J. L. Charles
C. K. Ellis
E. S. Gee
R. D. Kinser
A. C. Lilly
J. L. Myracle
E. B. Sanders
H. L. Spielberg

Figure 2



The figure illustrates the effects of smoking on P_1 latency. The latency differences among cigarettes is statistically significant ($p < .0001$). The latency difference between the dl- and l-nicotine cigarettes is not statistically significant ($p > .05$).

2022198666

References

1. Takada, K., Swedberg, M., Goldberg, S. and Katz, J. Discriminative stimulus effects of intravenous l-nicotine and nicotine analogs or metabolites in squirrel monkeys. Psychopharmacology. 99: 208-212; 1989.

2. Martin, B. R. Stereoselectivity of nicotine's central effects and its relationship to pain and cardiovascular function. In: Martin, W. R. et al., eds. Tobacco smoking and nicotine: a neurobiological approach. New York. Plenum Press 1987, 301-316.

3. Goldberg, S. R., Risner, M. E., Stolerman, I. P., Reavill, C. and Harbakhsh, S. G. Nicotine and some related compounds: effects on schedule-controlled behaviour and discriminative properties in rats. Psychopharmacology. 97: 295-302; 1989.

4. Paine, J. and Seeman, J. Purity of (R)-(+)-Nicotine. Memo to Gullotta, F.; 1990 February 13.

5. Secor, H. Notebook No. 7957, p. 52.

6. Martin, B. R. Notebook No. 8931, p. 9.

7. Gullotta, F. P. and Shultz, C. J. The effects of cigarette smoking on the electrical activity of the human brain: studies on the pattern-reversal evoked potential. Special Report 82-097; 1982 March 24.

8. Jasper, H. H. The ten-twenty electrode system of the International Federation. Electroencephalography and Clinical Neurophysiology. 10: 371-375, 1958.

F. P. Gullotta

C. A. Hayes

Bob Martin

2022198667